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## SARS: responding to an unknown virus

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**Abstract** The severe acute respiratory syndrome (SARS) is an emerging infection caused by a novel coronavirus which first appeared in southern China at the end of 2002. In early 2003, through a single incident, it spread to Hong Kong, Singapore, Canada and Vietnam. For busy clinicians in large public hospitals, the response to the virus was initially based on ensuring a high level of protection for staff. However, as the epidemic progressed and more information became available about the virus, procedures were rationalized and the virus is currently under control worldwide. There are, however, numerous unanswered questions concerning super-spreading events, the modes of transmission of the virus and, perhaps most importantly, the rapid detection of the virus early in the course of disease. These issues need to be addressed in case the virus becomes more widespread in the near future.

### Introduction

The severe acute respiratory syndrome (SARS) is a newly recognized coronavirus infection that emerged in southern China [1] with subsequent global spread to 29 countries [2–5]. In countries where local transmission has occurred, hospitals have been the major foci of infection especially in Singapore [6] and Canada [7]. In February 2003, reports began emerging on ProMed Mail of an outbreak of atypical pneumonia in the Guangdong province in southern China [8]. It is now believed that the first cases of SARS occurred in the city of Foshan in the Guangdong province [1]. However, throughout November until the late part of February, SARS was largely confined to the province of Guangdong.

The global dissemination of SARS is believed to have begun on the ninth floor of Hotel M in Hong Kong, where a physician from Guangdong stayed for one night on 22 February 2003 [9]. At least 16 individuals who were staying on the ninth floor of the hotel were subsequently infected with SARS, although none of them reportedly had direct contact with the ill physician. The newly infected individuals traveled onward to their homes or next destinations in the USA, Canada, Singapore, Hong Kong and Ireland sparking off epidemics of varying degrees of severity in each of those countries, mainly in hospitals but also in their respective communities. It is striking to realize that the entire global dissemination of this epidemic can probably be traced to this single event of one overnight hotel stay.

### Rapid scientific progress and an “outbreak” of publications

It has almost become a cliché to report that the SARS epidemic, the first emerging infectious disease of the 21st century, heralded an unprecedented collaboration between researchers across the globe. Within weeks of the first cases, electronic publications reviewed the clinical syndromes [4, 5] as well as the characteristics of the virus and methods for its detection by the polymerase chain reaction [2, 3]. The genome of various strains of the virus were sequenced, which contributed tremendously to knowledge of its molecular epidemiology [10]. There was an explosion of reports about the SARS coronavirus, with more than a thousand publications available on PubMed by the beginning of March 2004, the first anniversary of the global emergence of the virus. It is beyond the scope of this review to cover all of the virological and clinical information contained in these articles and I would refer the reader to the excellent review by Peiris et al. [11]. The present review focuses on the response to this emerging disease and its evolution in light of increasing information. Outstanding issues that remain to be resolved are also highlighted.

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## Nosocomial spread and the proliferation of guidelines

One of the first unusual aspects of this emerging infection was the recognition that healthcare workers (HCW) were uniquely susceptible to the then unknown etiologic agent. In Hong Kong, the first clue that a new infection had emerged was a cluster of ill HCWs. The same was noted in Vietnam and led to the World Health Organization (WHO) sending a team to Vietnam under the leadership of Dr Carlo Urbani, who later died from the virus he helped to define [12]. As soon as SARS was recognized as a nosocomial infection, guidelines were issued by various authorities including the WHO [13], the United States Centers for Disease Control and Prevention [14] and the Hong Kong Health Authority [15], Health Canada [16], and the Ministries of Health of Singapore [17] and Malaysia [18] among others. It is important to recognize that in the beginning of the SARS outbreak there was no information about the agent responsible for the infection or its mode of transmission; hence, there was a tendency to “over-protect.” As the epidemic evolved, so did the guidelines, which are constantly being updated and might indeed be out of date by the time this report is read. All guidelines are published on the internet [13–18], and the reader is encouraged to review the websites for the latest information.

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## Background: fears of pandemic influenza

The physician from Guangdong who became the source of the global epidemic through his stay at Hotel M was admitted to a hospital in Hong Kong the day after his arrival in the city. He became progressively more ill and died 10 days later. It is striking that although he was critically ill and intubated on a ventilator in the intensive care unit, only one HCW who attended to him in the emergency department became ill [19]. The reason for this is likely that Hong Kong hospitals had been on the alert for highly pathogenic avian influenza. In February, there had been a small cluster of cases of avian influenza in a Hong Kong family that had traveled to mainland China [20]. A directive had gone out from the Hong Kong Department of Health on 21 February 2003 to maintain strict infection control with droplet precautions for all cases of “atypical” community-acquired pneumonia because of concerns that highly pathogenic avian influenza might be easily transmissible from person to person.

One of the Singaporean women who returned from Hotel M was indeed isolated as a possible case of avian influenza in one of Singapore’s large general hospitals, and no secondary cases resulted from her. Because of the concerns for possible avian influenza, or some unknown pathogen with an uncertain mode of transmission, most of the initial strategies devised for the prevention and control of SARS were directed against a highly contagious airborne pathogen.

In 1997 [21], 18 previously healthy young people were infected and six died from highly pathogenic avian influenza in Hong Kong. This mortality rate (33%) is much higher than the normal mortality rate for influenza especially among young healthy individuals [22]. In response to the outbreak, more than one million chickens were slaughtered and the disease was rapidly brought under control. Seroepidemiologic studies of HCWs done at the time [23] demonstrated the efficacy of personal protective equipment (PPE) in preventing transmission and identified the risk associated with close personal contact in addition to the virus’s lack of efficient human-to-human transmission capability [21].

Fears of a recurrence of a more virulent or easily transmissible form of avian influenza directed the initial efforts against SARS. However, SARS possessed an unusual quality in that it seemed to be transmitted in the healthcare setting far more efficiently than in households, where measles, varicella and other airborne viruses usually take rapid hold [24]. This has yet to be explained completely, but it supports the argument that close contact is the major mode of transmission of the SARS virus.

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## Fomite transmission and obsessions with hygiene

Fomites have been a cause for concern with the SARS coronavirus since the initial global dissemination stemming from individuals in Hotel M who had no direct contact with the index case but had stayed in the same corridor and probably had occasion to touch elevator buttons or railings that might have been contaminated with the SARS virus. In the outbreak of SARS in the Amoy Gardens apartments in Hong Kong [25], more than 70 individuals who had no known direct contact were infected possibly through the aerosolisation of contaminated sewage. The implications of fomite transmission of SARS are considerable and would mandate a much greater degree of environmental cleaning than is currently practiced. However, there are many unanswered questions in this arena. For example, why did the individuals staying on the same hotel floor as the index case in Hotel M get infected but none of the staff? [9].

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## Coronaviruses and the implications for nosocomial spread of SARS

SARS has been convincingly demonstrated to be caused by a coronavirus [26]. Certain other characteristics have been ascertained from the previously known coronaviruses, 229E and OC43, including their ability to survive after drying on inanimate surfaces in the hospital environment as well as differences in the viability of the virus at different conditions of temperature and humidity [27, 28]. While the SARS coronavirus has a certain amount of homology with the other pathogenic human coronaviruses [10], too little is known about its behavior under different environmental and atmospheric conditions

to make a definitive statement about the role of the environment in nosocomial transmission. There have been reports of the SARS coronavirus persisting for prolonged periods of up to 2 days on environmental surfaces [29]. Survival in stool is reported to be even longer at up to 4 days in alkaline diarrheal stools. This would certainly help explain such circumstances as the Hotel M outbreak.

The attack rates for SARS have generally not been high. In Singapore, for example, the index case for the national outbreak was nursed in a general ward by staff who were not wearing protective covering of any kind, and the attack rate was only 1/8 doctors, 9/30 nurses and 1/12 fellow patients in the same ward areas [30]. Again, the distribution of infections suggests that close contact is the most important factor leading to the transmission of this pathogen in hospitals.

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### Personal protective equipment

The widespread emphasis on PPE has been seen by some as placing an undue emphasis on HCW protection without adequately considering the protection of other at-risk individuals, such as other patients in the same area. The use of PPE is also not without its own adverse consequences [31] as reactions to latex are common among HCWs, some with serious consequences. It should also be noted that the use of respirators has been associated with fatal adverse events [32]. Costs are also an issue, and in resource-poor settings 12-ply cotton masks have been used, which have reportedly been effective in preventing the nosocomial transmission of the virus in at least one large public hospital [33]. In a case-control study, Seto et al. [34] found that surgical masks were also effective in preventing transmission of SARS to HCWs, which is in line with our understanding of the epidemiology of the virus. In Singapore, one of the successes of our approach to the control of SARS was the widespread availability of full PPE for any staff member who requested it. This was even before the widespread dissemination of the virus led to the mandatory use of full PPE in all hospitals, and it provided staff the reassurance that their welfare was a high priority in the midst of an epidemic.

There have been concerns that the use of N95 masks alone might not be adequate for preventing the nosocomial transmission of SARS since cases have occurred among “fully protected” HCWs [35, 36]; these cases possibly resulted from contact transmission. Recognition of the role of contact transmission has led to the inclusion of recommendations for the use of gloves and gowns in all guidelines [13–18]. While these garments have been shown to be effective in preventing the nosocomial transmission of other respiratory viruses [37], few data are available for their efficacy regarding SARS.

### Airborne viruses and travel restrictions

Travel restrictions were among the more controversial aspects of the SARS epidemic. The economies of most affected countries in East Asia were devastated by these travel advisories. While other pathogens have been documented as being transmitted on airplanes, most notably influenza [38], the number of individuals infected with SARS during air travel was remarkably low. According to the WHO [39], there have been 35 flights carrying symptomatic probable SARS patients and 31 of those flights did not result in a single secondary infection. Overall, 27 cases of secondary infection resulted from symptomatic individuals. One flight alone, CA112, which flew from Hong Kong to Beijing on 15 March, is now known to have accounted for 22 of these 27 cases.

Olson et al. [40] reported that one flight with four symptomatic individuals with SARS was associated with an attack rate (for confirmed SARS) of zero while another flight with a single symptomatic individual was associated with an attack rate of 18%. The Singapore experience [41] was that three flights with symptomatic SARS patients resulted in only one transmission. The overall attack rate for the flights into Singapore was thus less than 1% despite one symptomatic individual being a so-called “super-spreader” and another being critically ill at the time of the flight, requiring intubation soon after arrival. Interestingly, Olson et al. [40] point out that fully 45% of the fellow passengers who became infected with SARS had no direct contact, as defined by the WHO, with the index patient on their ill-fated flight. They do not offer any explanation for the differing attack rates, although a careful reader would realize that among the 22 individuals allegedly infected on the flight, ten were traveling together as part of a tour group. Also, the flight with the four symptomatic individuals was much shorter than the flight that was associated with widespread transmission. This is supported by ICU data from Canada [42] that showed time of exposure to be a major risk factor. Overall, however, what these reports demonstrate is that a much more detailed analysis is required in order to truly understand the epidemiology of this unusual virus.

During the peak of the SARS epidemic in China (1–28 April 2003), when the WHO had travel advisories and alerts in place, there were more than 27,000 visitors from China and Hong Kong [43] who entered Singapore and not a single case of transmission was recorded from any of these individuals. In Taiwan, a strict 10-day quarantine [44] was placed on all individuals returning from countries that were on the WHO list of SARS-affected countries. A total of 80,813 individuals were quarantined, among whom 11 had probable SARS and only one of whom had laboratory-confirmed SARS. Thus, the detection rate was 0.01% for probable SARS and 0.001% for laboratory-confirmed SARS. These figures have to be balanced against the costs and psychological impact of quarantine for more than 80,000 individuals who were perfectly well.

Thanks to excellent isolation and case finding with contact tracing, the number of people infected with SARS

with each successive generation of the outbreak was progressively reaching extinction levels [45] in the SARS-affected countries. With the re-emergence of SARS at the beginning of 2004, drastic travel restrictions have fortunately not been instituted to date since there is no evidence yet of widespread dissemination of the virus across international air routes by travelers. It could also be argued that since we now have much better knowledge of the epidemiology of the virus, travel restrictions might not be necessary the next time around.

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### Engineering and administrative controls

All of the guidelines agree it would be ideal if patients with SARS could be nursed in isolation rooms [13–18]. There are differences, however, in the recommendations for negative pressure with separate ventilation systems, and these perhaps reflect the differences in resources available for healthcare. One drawback of isolation rooms is that unless there are adequate nursing or medical resources, the degree of attention that the patient will receive in a single isolation room is obviously lower than in an open well-ventilated area. Patients isolated for infection control purposes are known to be at risk for adverse events in hospital [46] and this again has to be balanced against the benefits in terms of reduced nosocomial transmission.

While all of the available evidence points to droplet and contact transmission, there is a possibility that the virus might be aerosolized during such procedures as high-flow oxygen therapy or possibly via the use of extractor fans, which were blamed for the aerosolisation of contaminated sewage during the Amoy Gardens outbreak [25]. Therefore, N95 respirators or higher should be used. This is a cause for concern as in many countries, including Singapore, without adequate pre-prepared negative-pressure rooms, powerful extractor fans similar to the ones used in the bathrooms at the Amoy Gardens apartments are used to create a form of laminar uni-directional airflow. While these may serve to direct the flow of air away from areas of heavy traffic, it is possible that they might be hazardous by facilitating the aerosolisation of infectious droplets.

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### Isolation and structural issues

In Singapore [47] and Canada [48], transmission of the SARS virus has been noted in crowded emergency rooms where patients routinely wait for hours for a hospital bed. In Singapore, SARS was documented as being transmitted to a patient's visitor who was waiting in a corridor during the patient's radiological procedure [49], again a common occurrence in many healthcare settings. In our own hospital, the National University Hospital, the largest cluster of SARS cases occurred in one of our eight-bed wards [47] where patients are deliberately placed eight to a cubicle in order to support the philosophy of healthcare

financing in Singapore. The SARS outbreak has clearly been a wake-up call for health authorities worldwide [50] as they try to adjust health systems primarily designed to minimize costs into systems designed to protect staff and patients. The isolation and segregation of patients with suspect and probable SARS has been credited with markedly reducing the transmission of the virus [45]. Lipsitch et al. [45] reported a reduction in the time to isolation of patients with SARS as the epidemic progressed with a corresponding decline in the number of secondary cases as knowledge of the virus increased.

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### Super-spreaders or super-spreading events?

The majority of individuals with SARS have not transmitted the virus to anyone [49]. While it is tempting to ascribe this to infection control measures, many of these individuals were infected and hospitalized long before the institution of infection control methods. This has given rise to the concept of "super-spreaders." It is known that the presence of common viral upper respiratory tract infections can turn some HCWs into so-called "cloud HCWs" [51]. These individuals have been linked with the airborne dispersal of agents that are normally only spread through contact, such as group A streptococci or *Staphylococcus aureus*. The hypothesis is that the presence of upper respiratory tract infections transforms these individuals into efficient transmitters of pathogens through increased coughing, sneezing or nose rubbing.

Alternatively, airborne dispersal could result from the use of various respiratory therapies. The index patient for the Singapore epidemic was not isolated, and 22 HCWs, visitors and fellow patients were infected [6]. The second generation of cases associated with this cluster, before the institution of infection control practices or strict isolation, included only 13 cases. The situation in Canada was similar, with cases in the second generation occurring pre-isolation [7]. It is quite clear, however, that non-isolated patients are hazardous to staff, visitors and other patients. Single non-isolated patients have led to well-documented outbreaks in hospitals in Singapore [49], Taiwan [52], Canada [53] and Hong Kong [54]. The phenomenon of "super-spreaders" has been invoked to explain why so few transmissions resulted from the majority of non-isolated individuals while a few rare cases were associated with the vast majority of transmissions [49]. The jury is still out as to whether these are indeed individuals who are for some reason more able to transmit infection or whether events, such as the use of high-flow oxygen therapy, are more responsible for what are probably more accurately described as "super-spreading events." Until we have more virologic information, we have to assume that all individuals with SARS are "super-spreaders" until proven otherwise and we have to take all the necessary precautions.

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## Whom to isolate?

Again, because of the concern that an undiagnosed patient might turn out to be a “super-spreader,” the threshold to isolation has become progressively lower. Initially, hospitals and clinics were using the WHO case definitions of suspect and probable SARS cases to determine which cases to isolate. As we, and others, have pointed out, atypical presentations [55] are the Achilles heel of such a strategy and these have been associated with significant nosocomial transmission. In a very important report from a SARS screening clinic, Rainer et al. [56] pointed out that the WHO criteria, which were actually designed for epidemiologic purposes, while relatively specific, have a sensitivity of only about 25% in predicting which individuals will turn out to have SARS. The implications are that a large number of individuals will need to be isolated and monitored very closely until their clinical course becomes evident. In practice in Singapore, this resulted in the conversion of large numbers of hospital wards to isolation facilities, cancellation of elective surgeries and an overall paralysis of the healthcare system. We used a regime of 4-hourly temperature monitoring without any use at all of antipyretics together with daily serial chest radiographs and blood counts and comprehensive chemistry work ups. With this regime, we found a sensitivity of 28%, specificity of 96%, positive predictive value of 11% and negative predictive value of 99% for the WHO criteria at patient presentation [57]. It is clear that an accurate rapid diagnostic test is urgently needed to allow us to filter out individuals who are at low risk of SARS or, better still, at lower risk of transmitting the virus should they not be isolated. Current diagnostic tests [58], which are based on either molecular methods or serological diagnosis, are severely limited not predominantly by sensitivity or specificity but by the fact that they take awhile to become positive, during which time widespread dissemination of the virus could have occurred from a single non-isolated “super-spreader.”

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## Fever screening

Fever screening is widely practiced as a SARS-prevention measure. There was even a period when the WHO called for fever screening at airports to prevent the global spread of SARS. Unfortunately, fever is a non-specific and insensitive screening tool for SARS [56]. Atypical presentations of SARS without fever have been reported especially in older and immunocompromised patients [59]. One case is particularly illustrative [47].

A 63-year-old man cleared a fever triage area in an emergency room as he was afebrile; he was then admitted to a general ward (not a “fever ward”) as a case of heart failure, and he remained afebrile until he developed a low-grade temperature after being transferred to the medical intensive care unit for progressive shortness of breath. Two other patients, one visitor and one nurse who had been in the same emergency department area as this

patient were infected with SARS. The visitor, a previously healthy 28-year-old woman, died and her husband and son were subsequently infected. In the brief period the index patient was in the general ward, two other patients and the entire shift of nurses working in the ward at the time, who were only wearing N95 masks, were infected. By the time the patient became febrile in the intensive care unit, staff were wearing full PPE and no further infections resulted. Thus, a single patient who “passed” two strict fever screens managed to be the source of at least nine infections in less than 24 h. This patient was critically ill and died 3 days later; thus, he may have had a very high viral load. This case illustrates the limitations of “cookbook screening” by using fever protocols without paying attention to a careful clinical history and physical examination. In this case, an alert cardiology team who re-did the patient’s history and examination and performed a bedside echocardiograph to prove that he was suffering from pneumonia not heart failure made the diagnosis.

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## Inter-hospital transfer of patients or viruses

During the SARS outbreak, the inter-hospital transfer of patients in Canada [53], Taiwan [52] and Singapore [6] was a very efficient means of dissemination of the SARS virus. In Singapore, on 22 March, the decision was made to close one hospital to new admissions and to concentrate all SARS patients there [6]. This unfortunately led to patients recently discharged from this hospital being shunted to other hospitals and starting off epidemics there. Now, in Singapore, once a cluster of cases with even a low degree of suspicion is identified, the unit is “locked down” with no admissions, transfers or discharges in order to prevent a recurrence of the former situation. This strategy was also used successfully in Vietnam to contain the SARS virus, which led to Vietnam being the first country to be declared free of local transmission of SARS [60].

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## Conclusion and research questions

While we have learned a tremendous amount in the brief period since SARS first emerged in November 2002, there are still a number of unresolved issues for practicing clinicians. The cases of SARS in early 2004 have quashed hopes that the virus was “put back in the box,” and in the formerly affected countries many clinicians are deeply worried about dealing with a devastating resurgence of the virus. I have a personal “wish list” of questions that I would like answered before too long. These include: what are the conditions required for the airborne transmission of the SARS coronavirus? When can we be sure that transmission does not occur? When can we get a good rapid diagnostic test that is positive early in the course of the illness? What makes a super-spreading event? Is quarantine really necessary? I can only hope that the answers to these and numerous other questions raised by

infection control practitioners, hospital epidemiologists, infectious disease clinicians and researchers can be answered before we face the next SARS outbreak or something worse! Even as this is being written, avian influenza rampages across East Asia affecting primarily birds, but also claiming the lives of more than 20 individuals. If this becomes a pandemic form of influenza, SARS will pale in comparison.

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